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(71) Applicant
John Wyeth and Brother Limited
(Great Britain)
Huntercombe Lane South
Taplow
Maidenhead
Berkshire SL6 0PH
(72) Inventors
John Leheup Archibald
Terence James Ward
(74) Agents
K J S Brown
c/o Wyeth Laboratories
Huntercombe Lane South
Taplow
Maidenhead
Berkshire SL6 0PH

(54) Benzoquinolizines

(57) The invention concerns N-methyl-N-(1,3,4,6,7,11bα-hexahydro-2*H*-benzo[alquinolizin-2β-yl)-*iso*-butanesulphonamide and the pharmaceutically acceptable acid addition salts thereof. The compounds possess high α_2-adrenoceptor antagonistic activity with a good α_2/α_1 adrenoceptor antagonistic selectivity.

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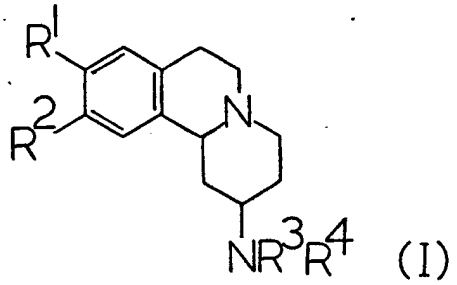
SPECIFICATION

Benzoquinolizines

This invention relates to benzoquinolizines, to process for preparing the benzoquinolizines and to pharmaceutical preparations containing them.

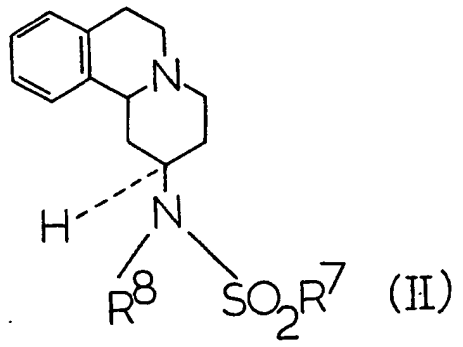
U.K. Patent specification No. 1,513,824 discloses that benzoquinolizines of the general formula (I)



(I)

and the pharmaceutically acceptable acid addition salts thereof, wherein R^1 and R^2 which may be the same or different,each represent hydrogen, lower alkyl, lower alkoxy orhalogen, R^3 represents hydrogen, lower alkyl or aryl and R^4 represents $-SO_2R^5$ (where R^5 is lower alkyl or aryl), $-CONH_2$ or $-CXNH^6$ (where X is oxygen or sulphur and R^6 is aryl or aryl. CO.), generally exhibit hypotensive activity upon administration to warm-blooded animals.

The specification of our U.K. Application No. 8125468 (published on 17th March 1982 under number 2083029A) discloses that benzoquinolizines of the general formula (II)



(II)

and the pharmaceutically acceptable acid addition salts thereof, wherein R^7 is lower alkyl or a phenyl or naphthyl group optionally substituted by one or more lower alkyl, lower alkoxy or halogen substitutents and R^8 is methyl or ethyl possess presynaptic α-adrenoceptor antagonistic activity in warm blooded animals.

We have now found that N-methyl-N-(1,3,4,6,7,11bα-hexahydro-2*H*-benzo[alquinolizin-2β-yl)-iso-butanesulphonamide, which is not disclosed specifically in either of the above mentioned specifications, together with its pharmaceutically acceptable acid addition salts, possesses extremely potent α-adrenoceptor antagonistic acitivity and high presynaptic selectivity. Accordingly the present invention provides N-methyl-N-(1,3,4,6,7,11bα-hexahydro-2*H*-benzo[alquinolizin-2β-yl)-*iso*-butanesulphonamide or a pharmaceutically acceptable acid addition salt thereof.

The presynaptic α-adrenoceptor antagonistic activity (or α_2 antagonsitic activity) of the compounds of the invention was investigated on the rat field stimulated vas deferens preparation using a modification of the method of Drew, Eur.J.Pharmac., 1977, *42*, 123–130. The procedure is described below.

Desheated vasa deferentia from sexually mature rats were suspended in a 6ml organ bath in Krebs solution at 37° and bubbled with 5% CO_2 in oxygen. Platinum ring electrodes were positioned above and below the tissue for field stimulation, the stimulus parameters being 0.1 Hz 1 ms pulse width at supramaximal voltage. Twitch responses were recorded isotonically with a 0.5 loading. Clonidine hydrochloride was used as the α-adrenoceptro agonist and cumulative concentration-response curves were constructed for the inhibition of twitch obtained with clonidine in the range 0.125 to 4 ng ml^{-1}. After washing out clonidine, the twitch response quickly recovered and an antagonist was then introduced into the Krebs reservior. Clonidine concentration-response curves were repeated 90 min after introduction of the antagonist. The concentration of clonidine producing 50% inhibition of twitch before and after introduction of antagonist were obtained and the dose-ratio for clonidine was calculated. Various concentrations of the antagonists were used.

These results were plotted in the manner described by Arunlakshana & Schild, Br.J.Pharmac. Chemother., 1959, *14*, 48–58 and the values of pA_2 and slope were calculated. The compound of the invention possesses potent presynaptic α-adrenoceptor antagonistic (α_2 antagonistic) activity having, a pA_2 value of 8.46 (95% confidence limits of 8.17–8.94), this value being higher than any of the values given for related compounds (including the isomeric *n*-butanesulphonamide) in the specification of U.K. Application No. 8125468.

The compound of the invention has been found to antagonise the presynaptic α-adrenoceptors to a much greater extent than the postsynaptic α-adrenoceptors. The postsynaptic antagonistic (or α_1 antagonistic) activity can be evaluated by a number of different methods. One method involves assessing the activity on the isolated anococcygeus muscle of the rat. The method is based on that of

Gillespie, Br.J.Pharmac., 1972, *45*, 404–416. In the procedure male rats (250–360g) are killed by a blow on the head and bled. The two anococcygeus muscles are removed from their position in the midline of the pelvic cavity, where they arise from the upper coccygeal vertebrae. The muscles are suspended in 5ml organ baths in Krebs solution containing 10^{-4}M ascorbic acid, to prevent drug oxidation. The tissues are gassed with a 95% oxygen, 5% CO_2 mixture and maintained at 37°. Longitudinal muscle contractions are recorded using isotonic transducers. Cumulative dose response curves are then obtained to phenylphrine or in some cases methoxamine, both agents being postsynaptic alpha adrenoceptor agonists. The concentration range of phenylephrine or methoxamine used in 0.02 to 0.8μg. ml^{-1}. The agonist is then washed from the bath and the test drug added to the bathing medium at a concentration of 10^{-6}M. After 30 min. equilibration with the test drug a further agonist dose response curve is obtained. The washing, equilibration and agonists dosing procedures are then repeated using 10^{-5}M and 10^{-4}M solutions of the test drug. Estimates of the pA_2 value for the test drug as an antagonist of phenylephrine or methoxamine were made from the agonist dose-ratios using the method of Arunlakshana & Schild, Br.J. Pharmac.Chemother., 1959, *14*, 48–58. The pA_2 for postsynaptic antagonistic activity for the compound of the invention was found to be 6.49 (with 95% confidence limits of 6.37–6.63). This means that the presynaptic selectivity (pA_2 presynaptic antagonists activity/pA_2 postsynaptic antagonistic activity) was 93 which should be contrasted with a presynaptic selectivity of 19 for the isomeric n-butanesulphonamide disclosed in U.K. Application No. 8125468.

The compound of the invention has good presynaptic α-adrenoceptor antagonistic acitivity with high presynaptic selectivity and is of value in conditions where selective antagonism of the α_2-adrenoceptor is desirable, for example, as an anti-depressant in treatment of diabetes and in inhibiting blood platelet aggregation. The compound of the invention has also been found to have 5-hydroxytryptamine (5-HT) antagonist activity. For example when tested in the rat isolated ileum the pA_2 for 5-HT antagonist activity was found to be 7.25.

The compounds of the present invention can be prepared by reacting a reactive derivative of isobutanesulphonic acid with 2β-methylamino-1,3,4,6,7,11b-hexahydro-2H-benzo[alquinolizine and, if required, converting a free base into a pharmaceutically acceptable acid addition salt. The reactive derivative of the sulphonic acid can be, for example, the acid halide or anhydride. Preferably it is the halide e.g. isobutanesulphonyl chloride. The reaction is preferably carried out under basic conditions, for example in the presence of a tertiary amine, e.g. triethylamine.

In an alternative procedure the compounds of the invention can be prepared by catalytic hydrogenation of N-methyl-N-(1,3,4,6,7,11bαhexahydro-2*H*-benzo[a]quinolizin-2β-yl)-2-methyl-2-propene-1-sulphonamide or an acid addition salt thereof and, if required, converting a free base into a pharmacuetically acceptable acid addition salt. The starting sulphonamide may be prepared by condensing 2β-methylamine-1,3,4,6,7,11b-hexahydro-2*H*-benzo[a]quinolizine with a reactive derivative of 2-methylprop-2-ene-1-sulponic acid, e.g. the sulphonyl chloride.

If in the processes described above the compound of the invention is obtained as an acid addition salt, the free base can be obtained by basifying a solution of the acid addition salt. Conversely, if the product of the process is a free base, an acid addition salt, particularly a pharmaceutically acceptable acid addition salt may be obtained by dissolving the free base in a suitable organic solvent and treating the solution with an acid, in accordance with conventional procedures for preparing acid addition salts from base compound.

Examples of acid addition salts are those formed from inorganic and organic acids, such as sulphuric, hydrochloric, hydrobromic, phosphoric, tartaric, fumaric, maleic, citric, acetic, formic, methanesulphonic and *p*-toluensulphonic acids.

The 2β-methylamino-1,3,4,6,7,11b-hexahydro-2H-benzo[a]quinolizine starting material can be prepared from the corresponding 2-oxo- compound by the procedure described in U.K. Patent Specification No. 513,824. Alternatively the 2-methylamino starting material can be prepared from the corresponding 2-amino compound, e.g. by reacting the amino compound with an alkylhalo-formate or with formic acid and reducing, e.g. with a hydride transfer reagent such as lithium aluminium hydride, the resulting 2-$NHCO_2$Alkyl or 2-NHCHO intermediate.

The invention further provides a pharmaceutical composition comprising N-methyl-N-(1,3,4,6,7,11bα-hexahydro-2*H*-benzo[a]quinolizin-2β-yl)-*iso*-butane sulphonamide or a pharmaceutically acceptable acid addition salt thereof is association with a pharmaceutically acceptable carrier. Any suitable carrier known in the art can be used to prepare the pharmacuetical composition. In such a composition, the carrier is generally a solid or liquid or a mixture of a solid and a liquid.

Solid form compositions include powders, granules, tablets, capsules (e.g. hard and soft gelatin capsules), suppositories and pessaries. A solid carrier can be, for example, one or more substances which may also act as flavouring agents, lubricants, solubilisers, suspending agents, fillers, glidants, compression

aids, binders or tablet-disintegrating agents; it can also be an encapsulating material. In powders the carrier is a finely divided solid which is in admixture with the finely divided active ingredient. In tablets the active ingredient is mixed with a carrier having the necessary compression properties in suitable proportions and compacted in the shape and size desired. The powders and tablets preferably contain up to 99%, e.g. from 0.03 to 99%, preferably 1 to 80% of the active ingredient. Suitable solid carriers include, for example, calcium phosphate, magnesium stearate, talc, sugars, lactose, dextrin, starch, gelatin, cellulose, methyl cellulose, sodium carboxylmethyl cellulose, polyvinylpyrrolidine, low melting waxes and ion exchange resins.

The term "composition" is intended to include the formulation of an active ingredient with encapsulating material as carrier to give a capsule in which the active ingredient (with or without other carriers) is surrounded by the carrier, which is thus in association with it. Similarly cachets are included.

Liquid form compositions include, for example, solutions, suspensions, emulsions, syrups, elixirs and pressurised compositions. The active ingredient, for example, can be dissolved or suspended in a pharmaceutically acceptable liquid carrier such as water, an organic solvent,a mixture of both or pharmaceutically acceptable oils or fats. The liquid carrier can contain other suitable pharmaceutical additives such as solubilizers, emulsifiers, buffers, preservatives, sweetners, flavouring agents, suspending agents, thickening agents, colours, viscosity regulators, stabilisers or osmo-regulators. Suitable examples of liquid carriers for oral and parenteral administration include water (particularly containing additives as above e.g. cellulose derivatives, preferably sodium carboxymethyl cellulose solution), alcohols (including monohydric alcohols and polyhydric alcohols e.g. gylcerol and glycols) and their derivatives, and oils (e.g fractionated coconut oil and arachis oil). For parenteral administration the carrier can also be an oily ester such as ethyl oleate and isopropyl myristate. Sterile liquid carriers are used in sterile liquid form compositions for parenteral adminstration.

Liquid phamaceutical compositions which are sterile solutions or suspensions can be utlised by, for example, intramuscular, intraperitoneal or subcutaneous injection. Sterile solutions can also be administered intravenously. When the compund is orally active it can be administered orally either in liquid or solid composition form.

Preferably the pharmaceutical composition is in unit dosage form, e.g. as tablets or capsules. In such form, the composition is sub-divided in unit doses containing appropriate quantities of the active ingredient; the unit dosage forms can be packaged compositions, for example packeted powders, vials, ampoules, prefilled syringes or sachets containing liquids. The unit dosage form can be, for example, a capsule or tablet itself, or it can be the appropriate number of any such compositions in package form. The quantity of the active ingredient in a dose of composition may be varied or adjusted from 0.5 mg or less to 750 mg or more, according to the particular need and the activity of the active ingredient. The invention also includes the compounds in the absence of the carrier where the compounds are in unit dosage form.

The following Example illustrates the invention:

EXAMPLE 1

N-Methyl-N-(1,3,4,6,7,11bα-hexahydro-2H-benzo[alquinolizin-2β-yl)-isobutanesulphonamide

(a) iso-Butanesluphonic acid, sodium salt, was prepared by hydrogenation of commercially available 2-methyl-2-propene-1-sulphonic acid, sodium salt, and converted to the sulphonyl chloride with $POCl_3$.

(b) An ice-cold, stirred solution of 2β-methylamino-1,3,4,6,7,11bα-hexahydro-2*H*-benzo[alquinolizine (2.16g; 0.01M) and triethylamine (1.2g; 0.012M) in dichloromethane (25 cm^3) was slowly treated with a solution of iso-butane-sulphonyl chloride (1.57g; 0.01M) in dichloromethane (25 cm^3). The clear solution was kept at room temperature for 6 days, washed with water (2 × 50 cm^3) and brine, dried ($MgSO_4$), filtered and evaporated to give a brown syrup (3.22 g). Chromatography on silica eluted with 10% ethanol-ethyl acetate gave a yellow oil (2.75 g) which was dissolved in hot ethanol (5 cm^3), acidified with ethanolic HCL, diluted with ethyl acetate (20 cm^3) and cooled. After anout ½ hour, the crystals were filtered off, washed with 10% ethanol/ethyl acetate and dried at 80°/100 mm to give pure title compound (2.40 g) as colourless cyrstals, m.p. 210-212° (dec).

CLAIMS

1. N-Methyl-N-(1,3,4,6,7,11bα-hexahydro-2*H*-benzo[alquinolizin-2β-yl)-*iso*-butanesulphonamide or a pharmaceutically acceptable acid addition salt thereof.

2. A process for preparing a compund claimed in claim 1 which comprises reacting a reactive derivative of iso-butanesulphonic acid with 2β-methylamino-1,3,4,6,7,11b-hexahydro-2*H*-benzo[a]quinolizine and, if required, converting a free base into a pharmaceutically acceptable acid addition salt.

3. A process for preparing a compund claimed in claim 1 which comprises catalytically hydrogenating N-methyl-N-(1,3,4,6,7,11bα-hexahydro-2*H*-benzo[a]quinolizin-2β-yl)-2-methyl-2-propene-1-sulphonamide or an acid addition salt thereof and if required,

converting a free base into a pharmaceutically acceptable acid addition salt.

4. A pharmaceutical composition having α_2-adrenoceptor antagonistic activity comprising N-methyl-N- (1,3,4,6,7,11bα-hexahydro-2*H*-benzo[a]quinolizin-2β-yl)-*iso*-butanesulphonamide or a pharmaceutically acceptable acid addition salt thereof in association with a pharmaceutically acceptable carrier.

5. A process for preparing a compound claimed in claim 1 substantially as hereinbefore described with reference to Example 1.

6. A compund whenever prepared by the process of any one of claims 2,3, and 4.

7. N-Methyl-N-(1,3,4,6,7,11bα-hexahydro-2*H*-benzo[a]quinolizin-2β-yl)-*iso*-butanesulphonamide or a pharmaceutically acceptable acid addition salt thereof for use in antagonising α_2-adrenoceptors in warm blooded animals.

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